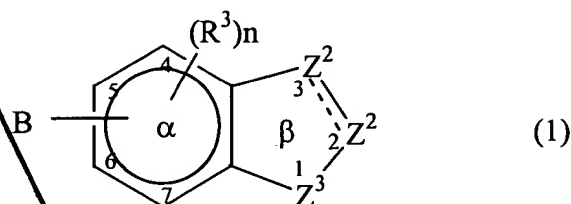


Claims

1. A compound of the formula:



and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein

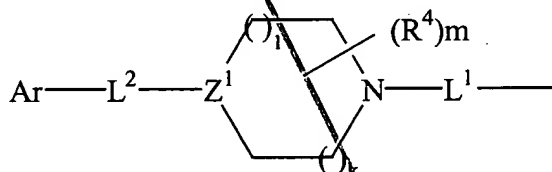
--- represents a single or double bond;

B is $-W_i-\text{COX}_jY$ wherein Y is COR^2 or an isostere thereof and R^2 is hydrogen or a noninterfering substituent, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1;

each R^3 is independently a noninterfering substituent, where n is 0-3;

Z^3 is NR^7 or O; wherein R^7 is H or a noninterfering substituent;

one Z^2 is CA or CR^8A and the other is CR^1 , CR^1_2 , NR^6 or N wherein each R^1 , R^6 and R^8 is independently hydrogen or noninterfering substituent; wherein A is:



such that Z^1 is CR^5 or N wherein R^5 is hydrogen or a noninterfering substituent;

each of l and k is an integer from 0-2 wherein the sum of l and k is 0-3;

Ar is an aryl group substituted with 0-5 noninterfering substituents, wherein two noninterfering substituents can form a fused ring;

each R^4 is independently a noninterfering substituent where m is 0-4;

each of L^1 and L^2 is a linker; and

the distance between the atom of Ar linked to L^2 and the center of the β ring is 4.5-24Å.

2. The compound of claim 1 wherein B is $-\text{COXjCOR}^2$, and
 wherein R^2 is H, or is straight or branched chain alkyl, alkenyl, alkynyl, aryl,
 arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted with
 halo, alkyl, heteroalkyl, SR, OR, NR_2 , OCOR, NRCOR, NRCONR_2 , NRSO_2R ,
 NRSO_2NR_2 , OCONR_2 , CN, COOR, CONR_2 , COR, or R_3Si wherein each R is
 independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, or
 wherein R^2 is OR, NR_2 , SR, NRCONR_2 , OCONR_2 , or NRSO_2NR_2 , wherein each R
 is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, and
 wherein two R attached to the same atom may form a 3-8 member ring and wherein said
 ring may further be substituted by alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl,
 heteroaryl, heteroarylalkyl, each optionally substituted with halo, SR, OR, NR_2 , OCOR,
 NRCOR, NRCONR_2 , NRSO_2R , NRSO_2NR_2 , OCONR_2 , or R_3Si wherein each R is
 independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof
 wherein two R attached to the same atom may form a 3-8 member ring, optionally
 substituted as above defined; and
 X, if present, is alkylene.

3. The compound of claim 1 wherein Y is an isostere of COR^2 .

4. The compound of claim 3 wherein Y is tetrazole; 1,2,3-triazole;
 1,2,4-triazole; or imidazole.

5. The compound of claim 1 wherein each of i and j is 0.

6. The compound of claim 2 wherein j is 0.

7. The compound of claim 1 wherein Z^3 is NR^7 .

8. The compound of claim 7 wherein R^7 is H or is optionally substituted
 alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl,
 heteroalkynyl, heteroalkylaryl, or is SOR, SO_2R , RCO, COOR, alkyl-COR, SO_3R ,
 CONR_2 , SO_2NR_2 , CN, CF_3 , NR_2 , OR, alkyl-SR, alkyl-SOR, alkyl- SO_2R , alkyl-OCOR,

alkyl-COOR, alkyl-CN, alkyl-CONR₂, or R₃Si, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof.

9. The compound of claim 8 wherein R⁷ is H, or is optionally substituted alkyl, or acyl.

10. The compound of claim 1 wherein both k and l are 1.

11. The compound of claim 1 wherein L¹ is CO, CHOH or CH₂.

12. The compound of claim 11 wherein L¹ is CO.

13. The compound of claim 1 wherein Z¹ is N.

14. The compound of claim 1 wherein Z¹ is CR⁵ wherein R⁵ is H, OR, NR₂, SR or halo, wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof,

15. The compound of claim 1 wherein L² is alkylene (1-4C) or alkenylene (1-4C) optionally substituted with a moiety selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR₂, SR, SOR, SO₂R, OCOR, NRCOR, NRCONR₂, NRCOOR, OCONR₂, RCO, COOR, alkyl-OOR, SO₃R, CONR₂, SO₂NR₂, NRSO₂NR₂, CN, CF₃, R₃Si, and NO₂, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two substituents on L² can be joined to form a non-aromatic saturated or unsaturated ring that includes 0-3 heteroatoms which are O, S and/or N and which contains 3 to 8 members or said two substituents can be joined to form a carbonyl moiety or an oxime, oximeether, oximeester or ketal of said carbonyl moiety.

16. The compound of claim 15 wherein L² is unsubstituted alkylene.

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17. The compound of claim 15 wherein L^2 is unsubstituted methylene, methylene substituted with alkyl, or $-CH=$.

5 18. The compound of claim 1 wherein Ar is optionally substituted with 0-5 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2 , SR, SOR, SO_2R , OCOR, NRCOR, $NRCONR_2$, $NRCOOR$, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R , $CONR_2$, SO_2NR_2 , $NRSO_2NR_2$, CN, CF_3 , R_3Si , and NO_2 , wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said optional substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated

10 ring which contains 3-8 members.

19. The compound of claim 18 wherein Ar is optionally substituted phenyl.

20. The compound of claim 19 wherein said optional substitution is by halo, OR, or alkyl.

15 21. The compound of claim 20 wherein said phenyl is unsubstituted or has a single substituent.

20 22. The compound of claim 1 wherein R^4 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2 , SR, SOR, SO_2R , OCOR, NRCOR, $NRCONR_2$, $NRCOOR$, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R , $CONR_2$, SO_2NR_2 , $NRSO_2NR_2$, CN, CF_3 , R_3Si , and NO_2 , wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R^4 on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members, or R^4 is $=O$ or an oxime, oximeether, oximeester or ketal thereof.

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23. The compound of claim 22 wherein each R^4 is halo, OR, or alkyl.

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24. The compound of claim 23 wherein m is 0, 1, or 2.
25. The compound of claim 24 wherein m is 2 and both R⁴ are alkyl.
26. The compound of claim 1 wherein each R³ is halo, alkyl, heteroalkyl, OCOR, OR, NRCOR, SR, or NR₂, wherein R is H, alkyl, aryl, or heteroforms thereof.
27. The compound of claim 26 wherein R³ is halo or alkoxy.
28. The compound of claim 27 wherein n is 0, 1 or 2.
29. The compound of claim 1 wherein L¹ is coupled to the β ring at the 5-position.
30. The compound of claim 1 wherein Z² at position 3 is CA or CH¹A.
31. The compound of claim 30 wherein the Z² at position 2 is CR¹ or CR¹₂.
32. The compound of claim 31 wherein R¹ is hydrogen, or is alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR₂, SR, SOR, SO₂R, OCOR, NRCOR, NRCONR₂, NRCOOR, OCONR₂, RCO, COOR, alkyl-OOR, SO₃R, CONR₂, SO₂NR₂, NRSO₂NR₂, CN, CF₃, R₃Si, and NO₂, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R¹ can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.
33. The compound of claim 32 wherein each R¹ is selected from the group consisting of H, alkyl, acyl, aryl, arylalkyl, heteroalkyl, heteroaryl, halo, OR, NR₂, SR, NRCOR, alkyl-OOR, RCO, COOR, and CN, wherein each R is independently H, alkyl, or aryl or heteroforms thereof.

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34. The compound of claim 30 wherein Z^2 at position 2 is N or NR^6 .

35. The compound of claim 34 wherein R^6 is H, or alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, or is SOR, SO_2R , RCO, COOR, alkyl-COR, SO_3R , $CONR_2$, SO_2NR_2 , CN, CF_3 , or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof.

36. The compound of claim 1 wherein  represents a double bond.

37. The compound of claim 1 wherein the distance between the atom on Ar linked to L^2 and the center of the β ring is 7.5-11 Å.

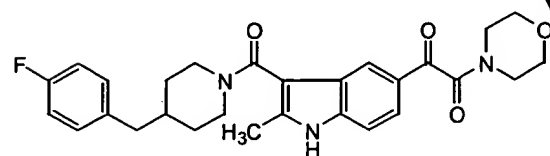
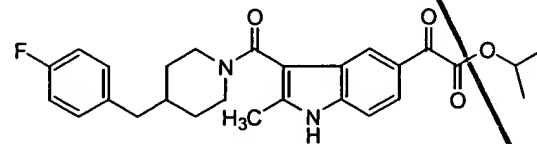
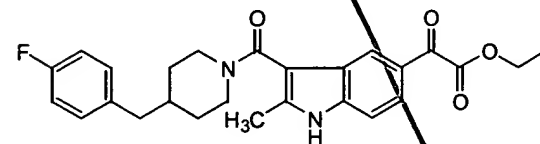
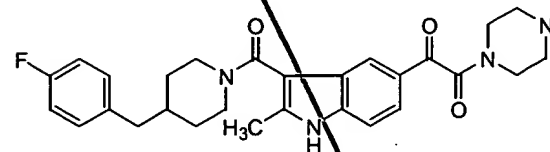
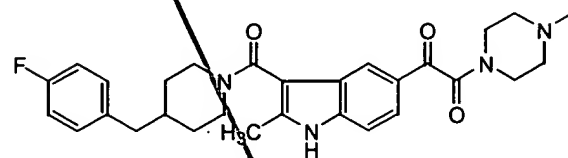
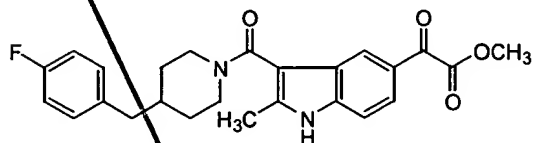
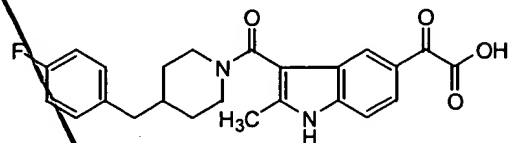
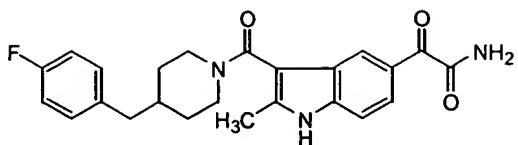
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38. The compound of claim 1 wherein the compound of formula (1) is selected from the group consisting of:

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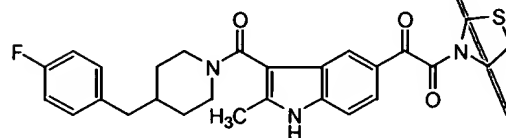
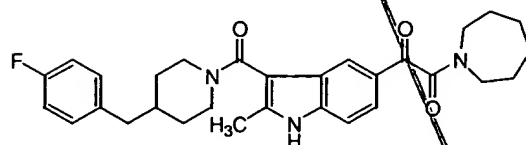
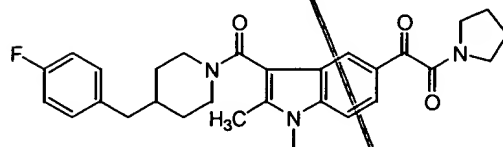
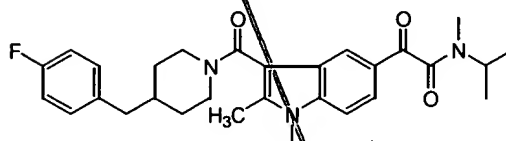
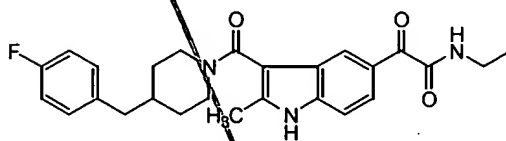
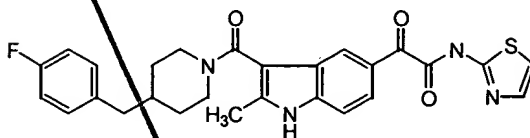
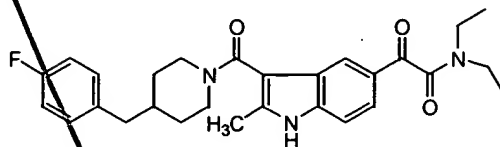
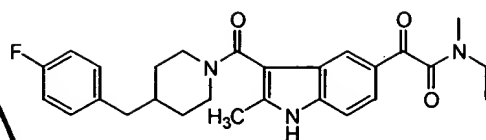
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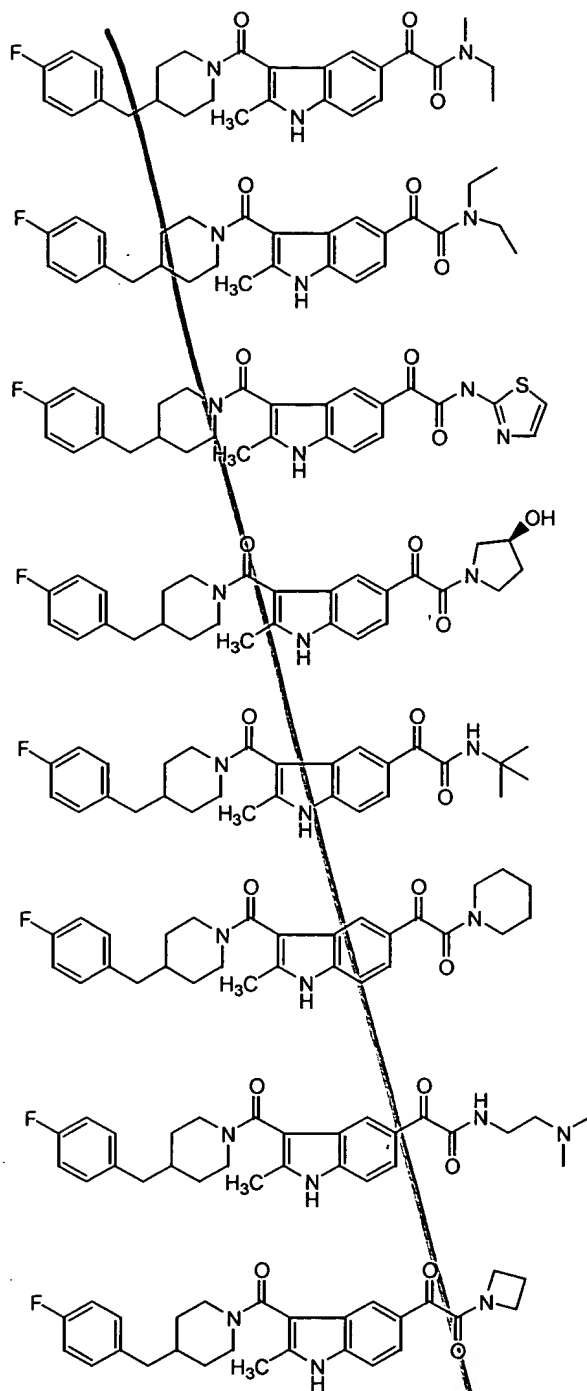
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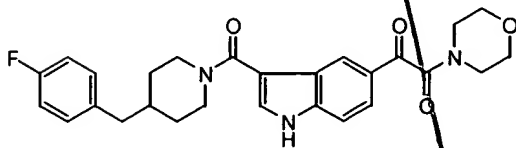
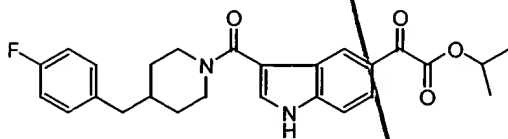
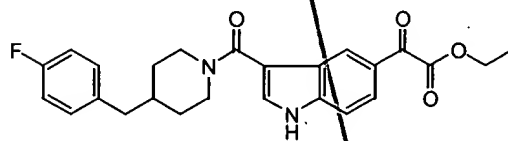
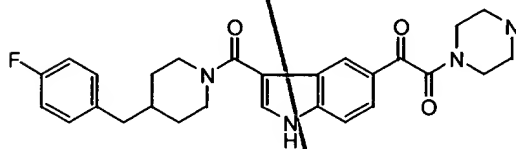
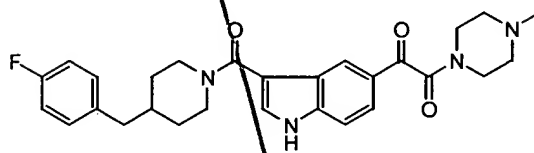
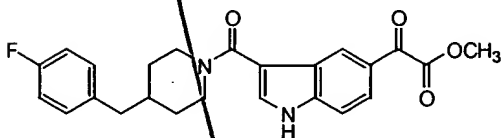
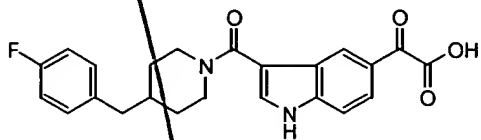
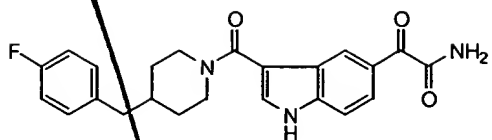
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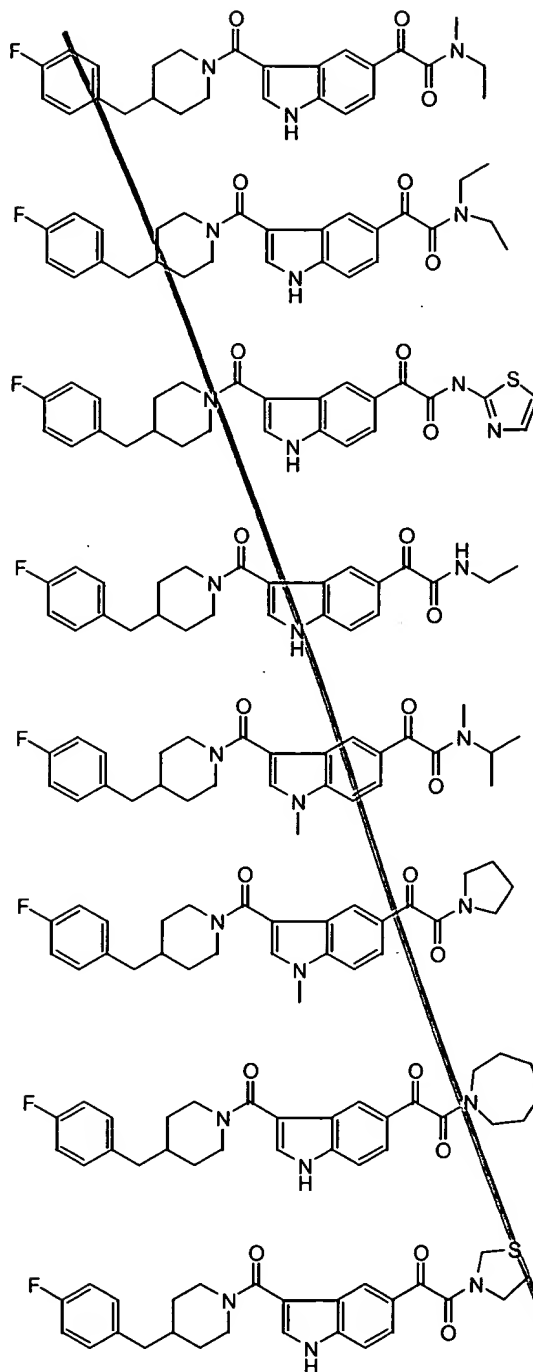
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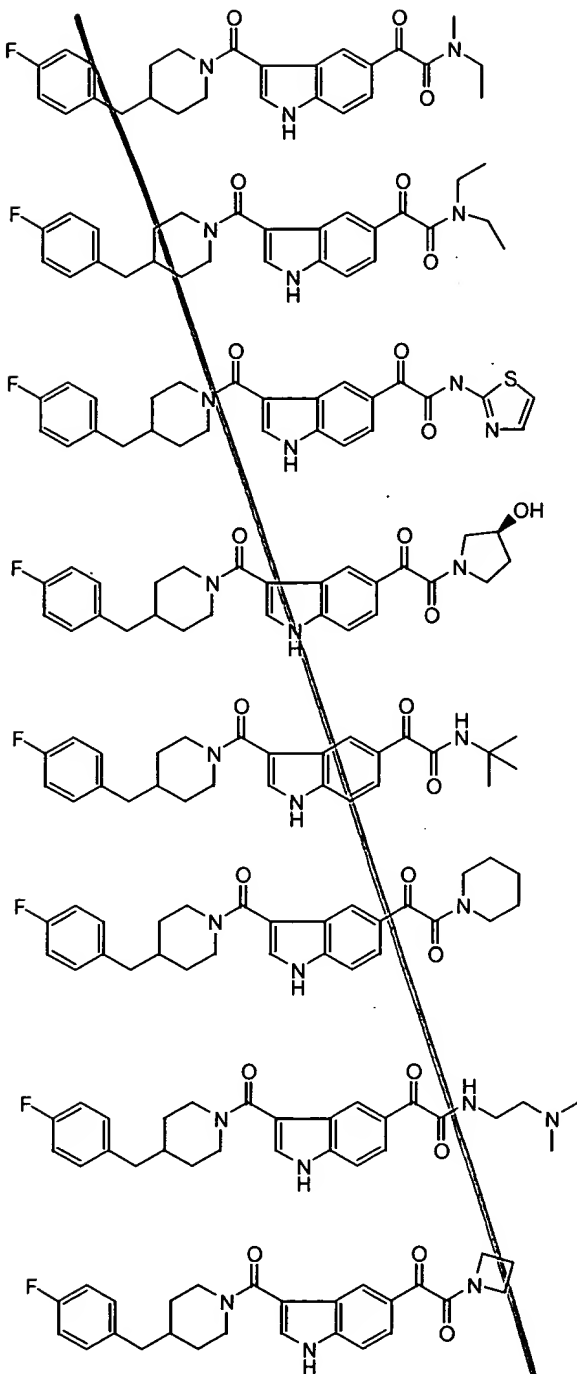
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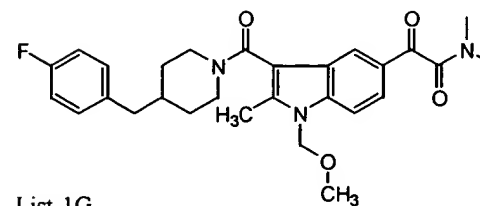
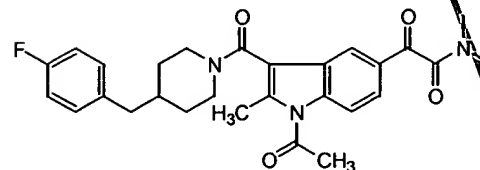
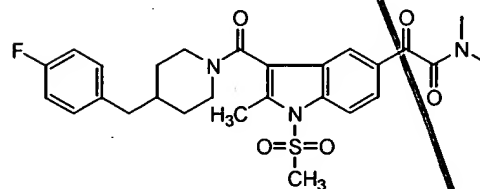
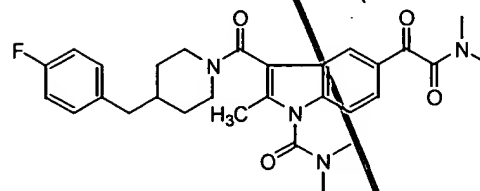
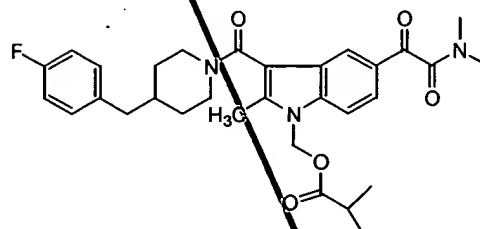
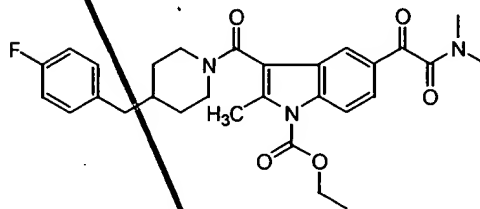
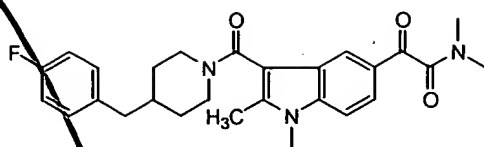
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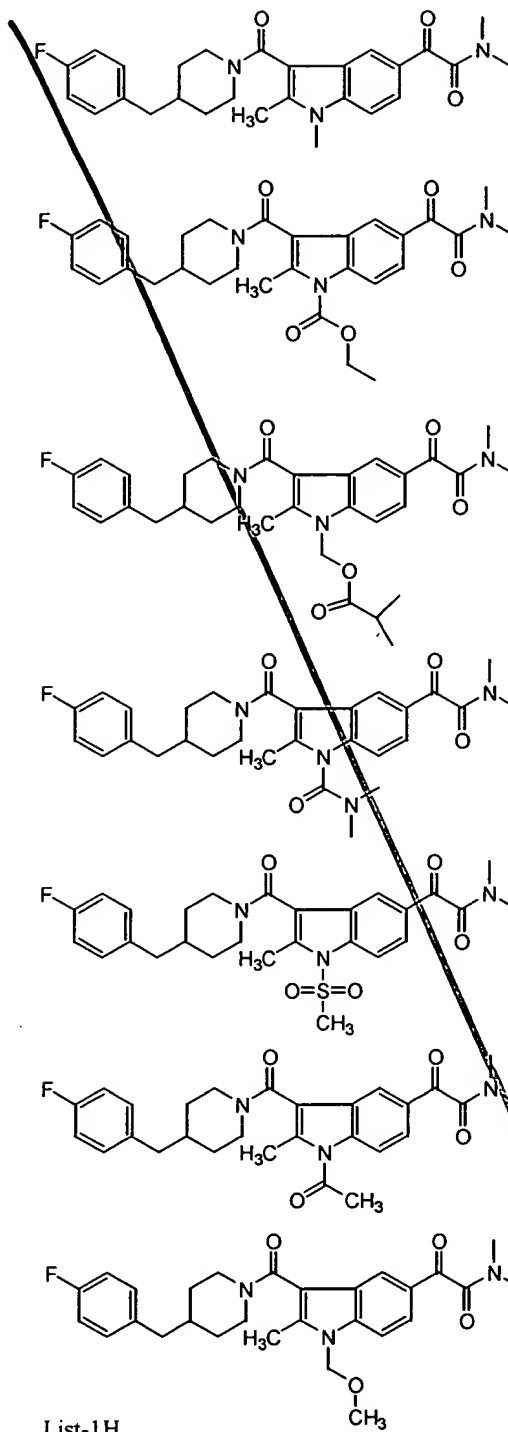
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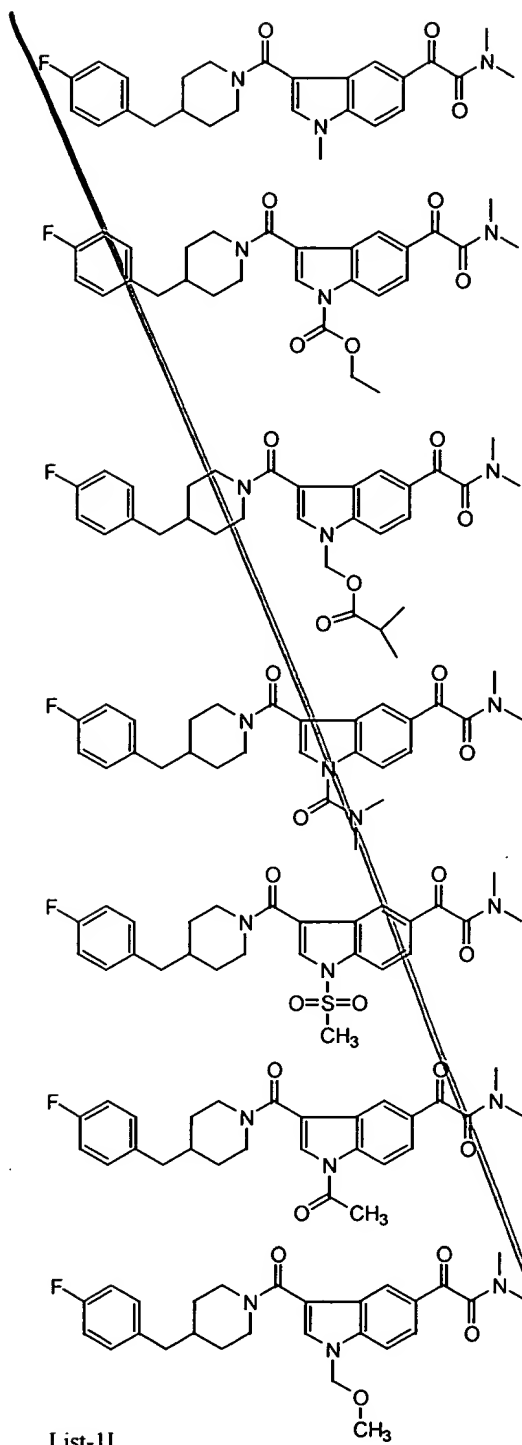
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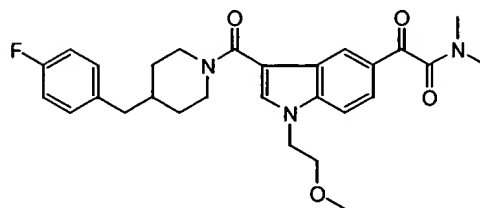
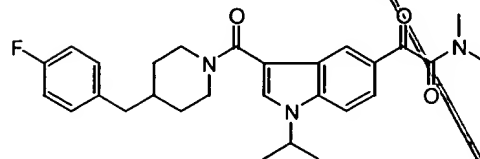
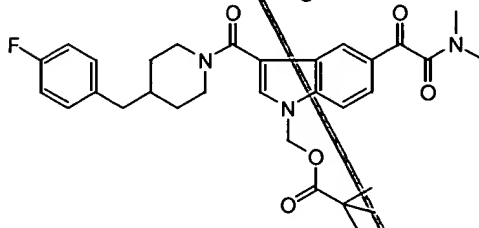
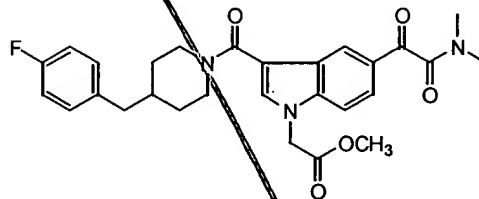
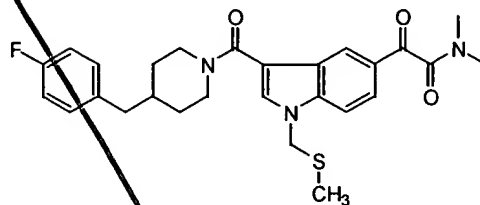
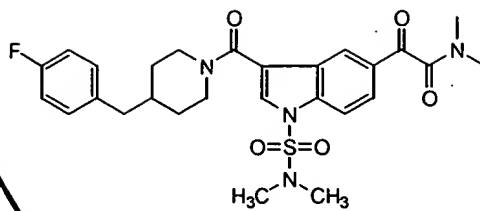
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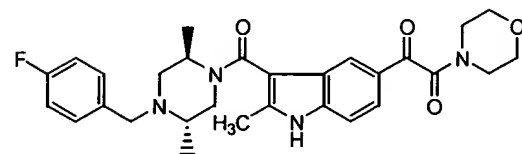
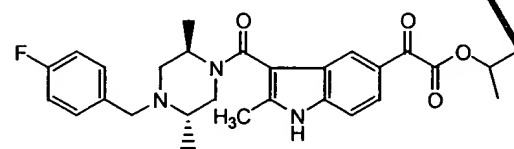
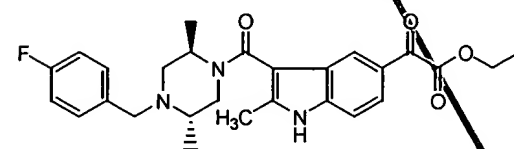
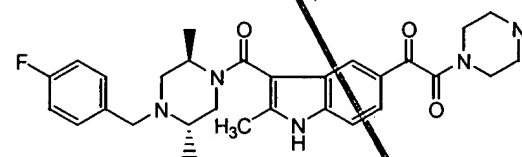
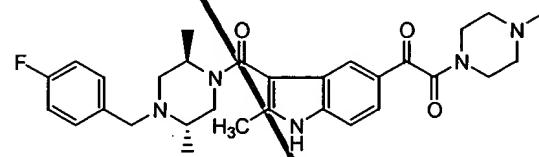
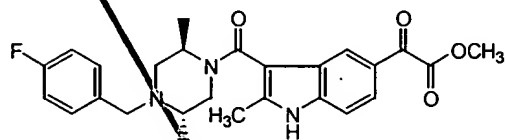
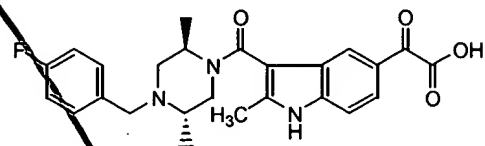
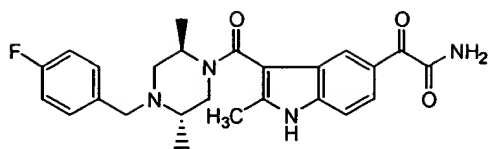
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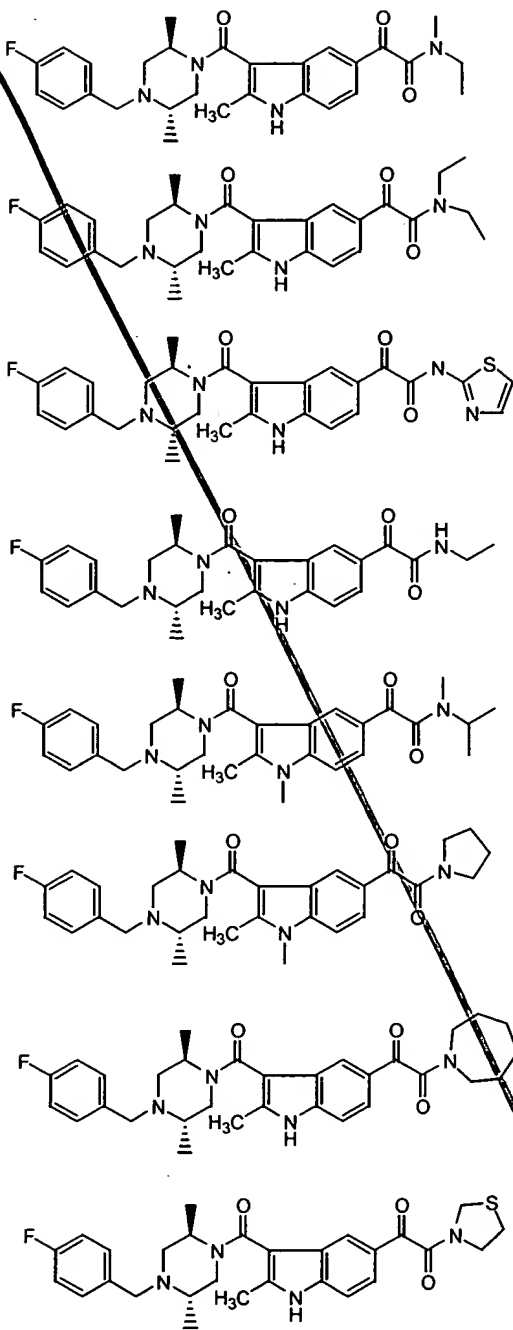
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List-1J

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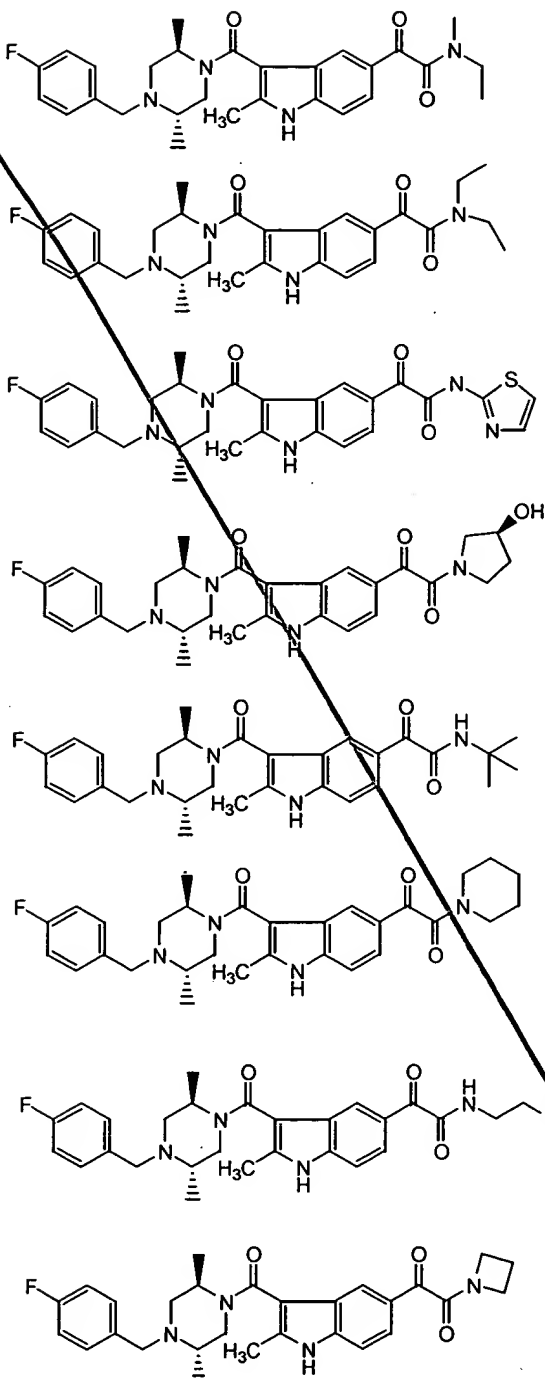
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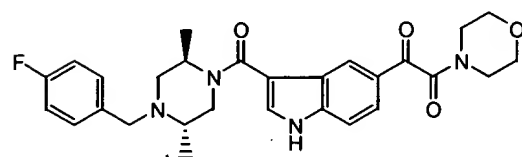
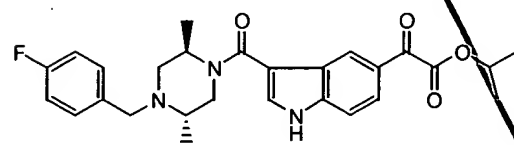
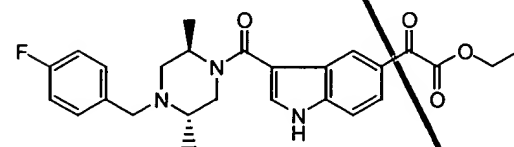
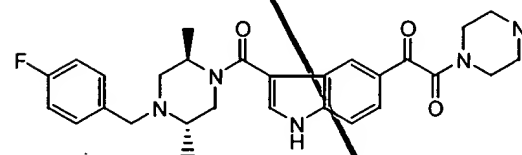
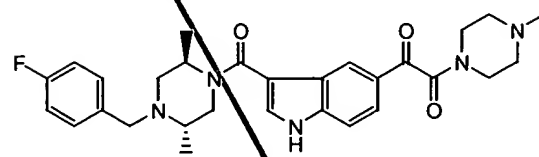
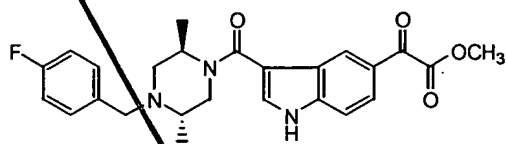
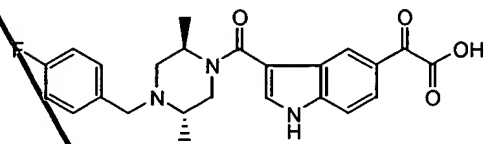
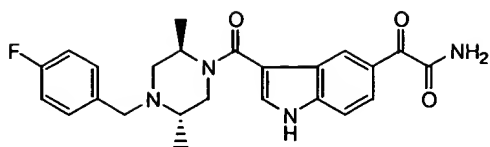
List -2B

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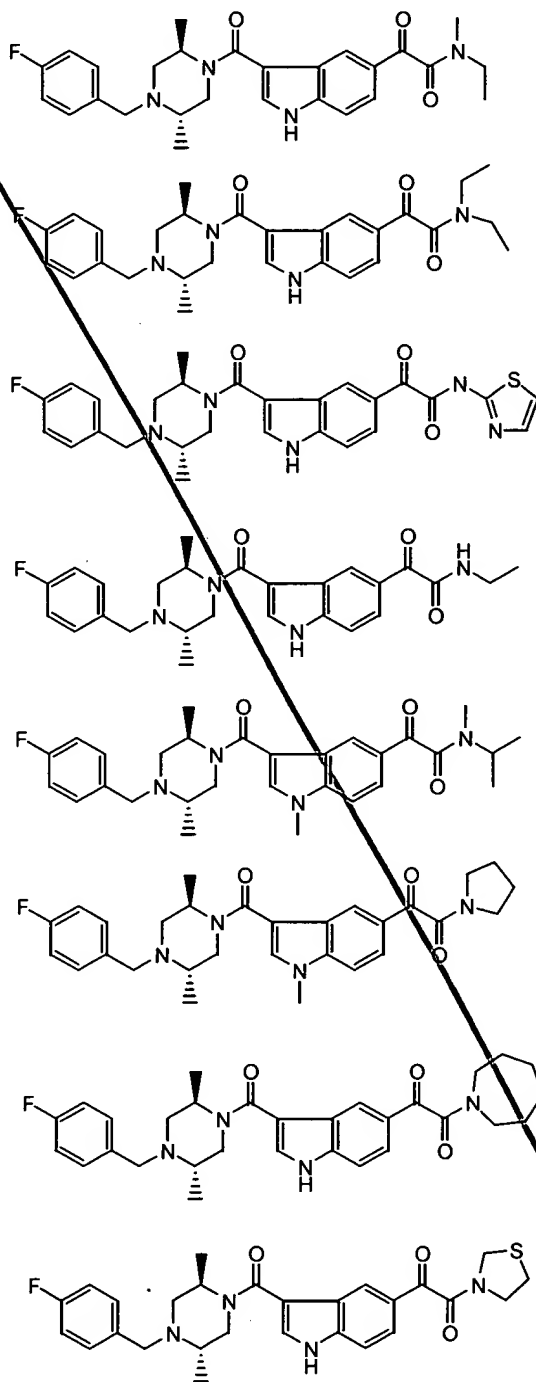
FOUO 187-11900

a¹
cont

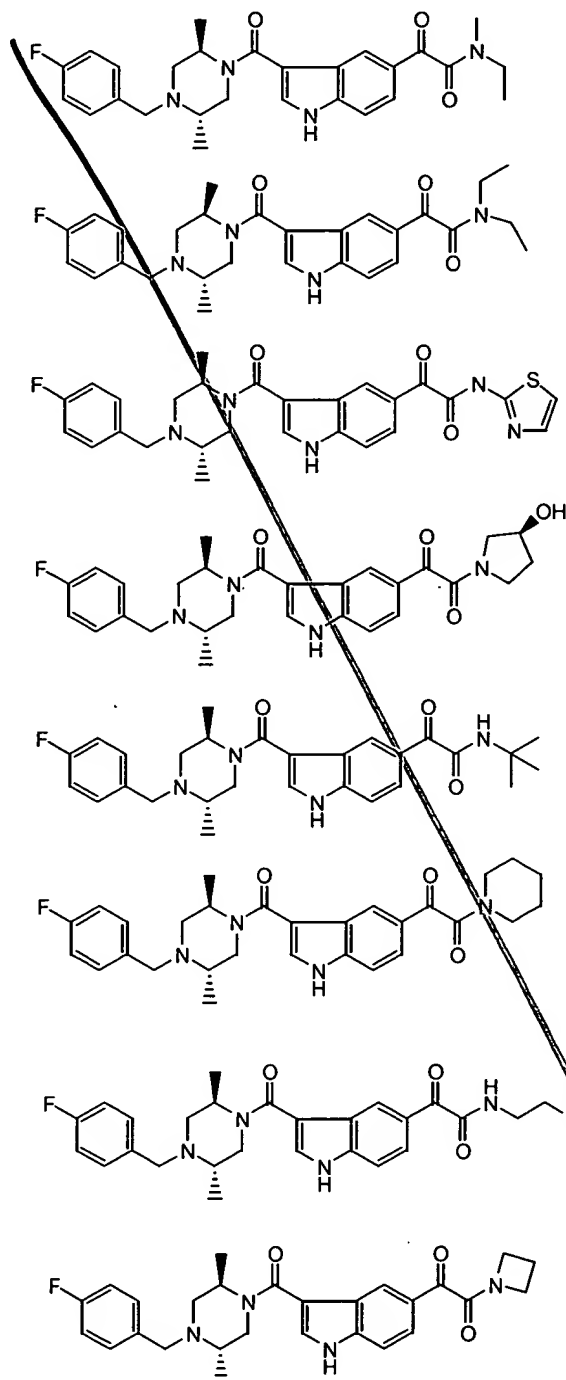
List -2C

a'
cont

List-2D

a'
cont

List -2E

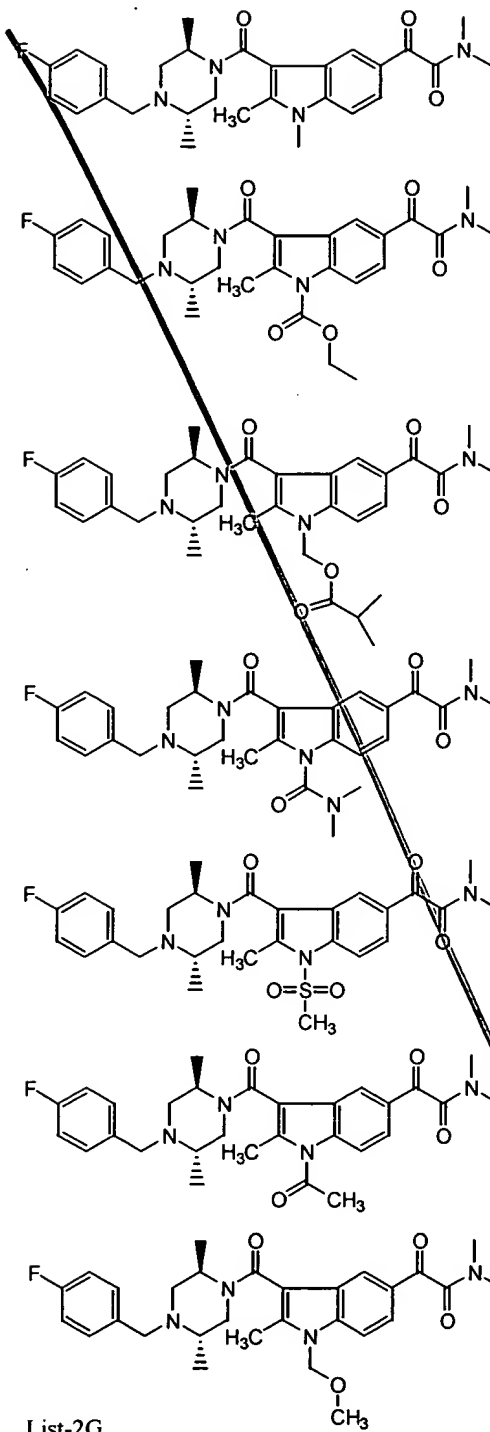
a!
cont

List -2F

09990187 112001

a'
cont

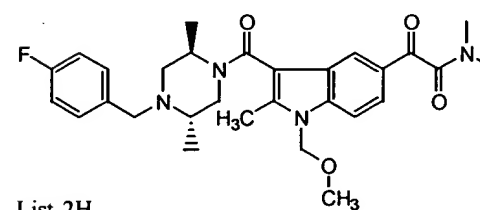
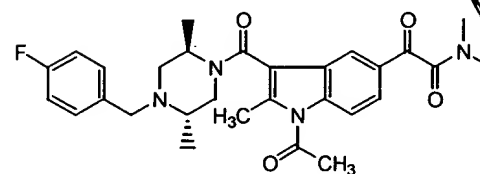
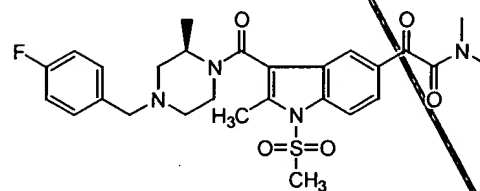
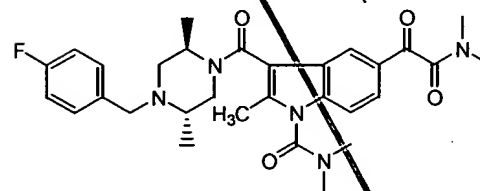
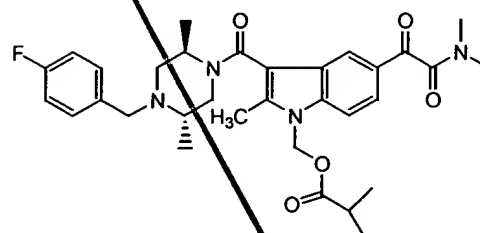
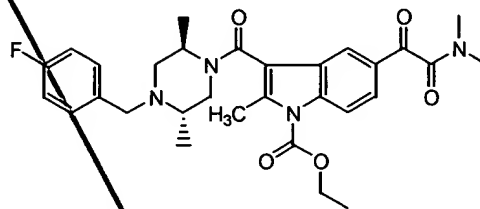
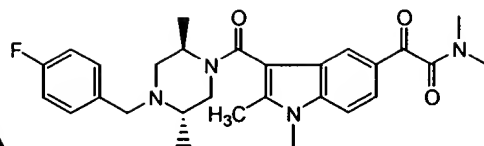
FOUO " 28T06560



List-2G

Q1
cont

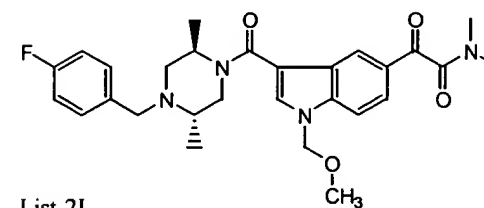
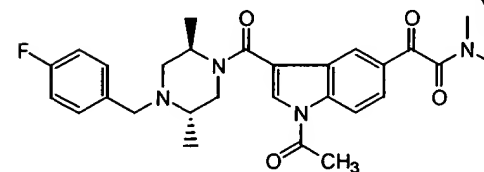
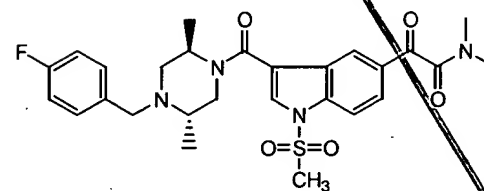
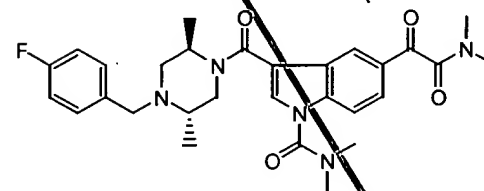
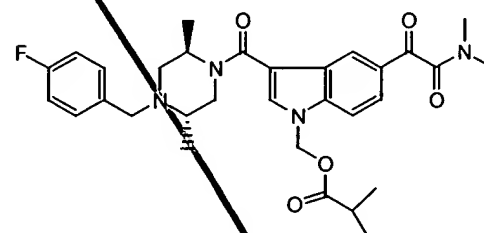
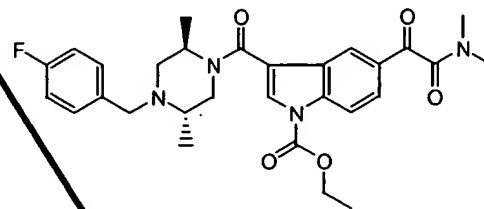
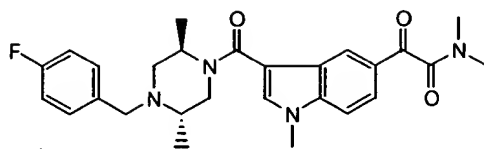
FOUO " 187 11001



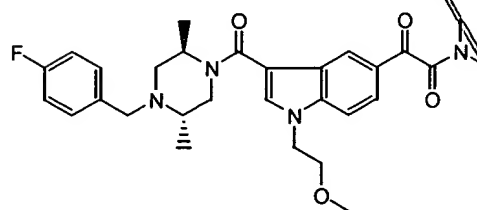
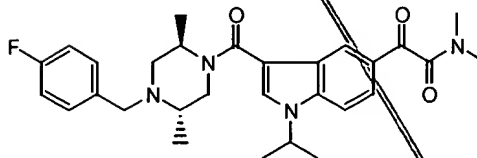
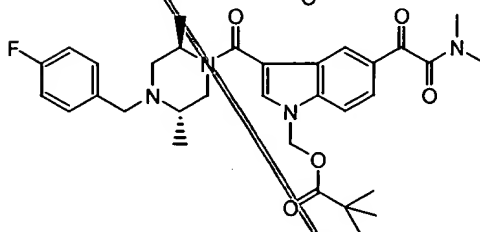
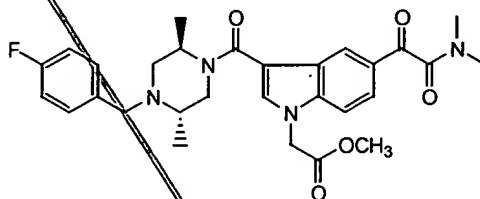
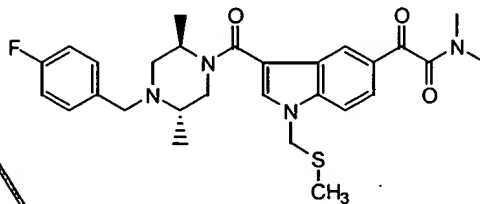
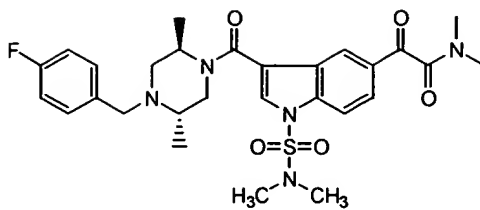
List-2H

a'
cont

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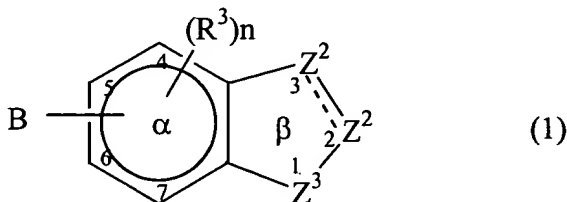
List-21

a'
cont

List-2J

39. A pharmaceutical composition for treating conditions characterized by enhanced p38- α activity which composition comprises

a therapeutically effective amount of a compound of the formula



5 and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein

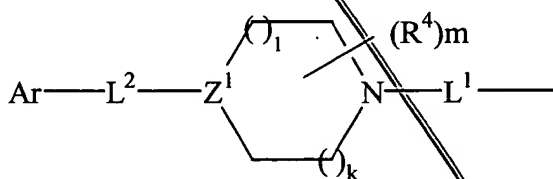
\equiv represents a single or double bond;

B is $-W_i-CO-X_j-Y$ wherein Y is COR^2 or an isostere thereof and R^2 is hydrogen or a noninterfering substituent, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1;

each R^3 is independently a noninterfering substituent, where n is 0-3;

Z^3 is NR^7 or O; wherein R^7 is H or a noninterfering substituent;

one Z^2 is CA or CR^8A and the other is CR^1 , CR^2 , NR^6 or N wherein each R^1 , R^6 and R^8 is independently hydrogen or noninterfering substituent; wherein A is:



such that Z^1 is CR^5 or N wherein R^5 is hydrogen or a noninterfering substituent;

each of l and k is an integer from 0-2 wherein the sum of l and k is 0-3;

Ar is an aryl group substituted with 0-5 noninterfering substituents, wherein two noninterfering substituents can form a fused ring;

each R^4 is independently a noninterfering substituent where m is 0-4;

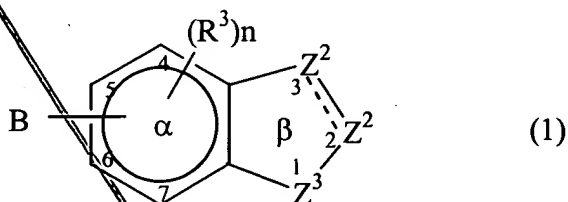
each of L^1 and L^2 is a linker; and

the distance between the atom of Ar linked to L^2 and the center of the β ring is 4.5-24Å.

40. The composition of claim 39 which further contains an additional therapeutic agent.

41. The composition of claim 40 wherein said additional therapeutic agent is a corticosteroid, a monoclonal antibody, or an inhibitor of cell division.

42. A method to treat a condition mediated by p38- α kinase comprising administering to a subject in need of such treatment a compound of the formula:



and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein

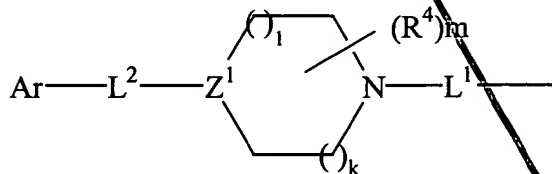
represents a single or double bond;

B is $-W_i-CO-X_j-Y$ wherein Y is COR^2 or an isostere thereof and R^2 is hydrogen or a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;

each R^3 is independently a noninterfering substituent, where n is 0-3;

Z^3 is NR^7 or O; wherein R^7 is H or a noninterfering substituent;

one Z^2 is CA or CR^8A and the other is CR^1 , CR^2 , NR^6 or N wherein each R^1 , R^6 and R^8 is independently hydrogen or noninterfering substituent; wherein A is:



such that Z^1 is CR^5 or N wherein R^5 is hydrogen or a noninterfering substituent;

each of l and k is an integer from 0-2 wherein the sum of l and k is 0-3;

Ar is an aryl group substituted with 0-5 noninterfering substituents, wherein two noninterfering substituents can form a fused ring;

each R^4 is independently a noninterfering substituent where m is 0-4;

each of L^1 and L^2 is a linker; and
the distance between the atom of Ar linked to L^2 and the center of the β ring
is 4.5-24Å.

Q1
cont

43. The method of claim 42 wherein said condition is a proinflammation
response.

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44. The method of claim 43 wherein said proinflammation response is
multiple sclerosis, IBD, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty
arthritis, other arthritic conditions, sepsis, septic shock, endotoxic shock, Gram-negative
sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke,
reperfusion injury, CNS injury, psoriasis, restenosis, cerebral malaria, chronic pulmonary
inflammatory disease, silicosis, pulmonary sarcosis, a bone resorption disease, graft-
versus-host reaction, Crohn's Disease, ulcerative colitis, Alzheimer's or pyresis.

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